Public Health England

Health Protection Report
weekly report

## Infection report

**Volume 9 Number 21 Published on: 19 June 2015**

### Bacteraemia

# Voluntary surveillance of *Klebsiella* spp. bacteraemia in England, Wales and Northern Ireland: 2010-2014

These analyses are based on data relating to diagnoses of *Klebsiella* spp. bloodstream infections during 2010-2014 in England, Wales and Northern Ireland (EWNI) extracted from Public Health England's (PHE) voluntary surveillance database Second Generation Surveillance System (SGSS).

SGSS comprises a communicable disease module (CDR; formerly CoSurv/LabBase2) and an antimicrobial resistance module (AMR; formerly AmSurv). Most analyses presented here are based on data extracted from the CDR module of SGSS data on 5 June 2015, except for the evaluation of multi-drug resistance data from the antimicrobial resistance (AMR) module of SGSS (data extracted 15 June 2015). This module captures more comprehensive antibiogram data allowing more robust evaluation of multi-resistance rates. However these data cannot be used for the trend analysis due to lower laboratory coverage in previous years.

The data presented here will differ in some instances from those in earlier publications partly due to the inclusion of late reports.

Rates of bacteraemia laboratory reports were calculated using mid-year resident population estimates for the respective year and geography, with the exception of 2014 rates, which were based on 2013 population estimates as population estimates for 2014 were not available at the time of producing this report [1,2]. Geographical analyses were based on the residential postcode of the patient if known (otherwise the GP postcode if known or failing that the postcode of the laboratory) with cases in England being assigned to the catchment area of one of 15 local PHE centres (PHECs) formed from administrative local authority boundaries.

This report includes analyses of the trends, patient demographic and geographical distribution as well as antimicrobial susceptibility among these bacteraemia episodes.

## Key points

- between 2013 and 2014 the total number of reports of *Klebsiella* spp. bacteraemia in EWNI increased by 0.8% (from 6,453 to 6,507 episodes), an increase in population rate from 10.98 to 11.07 per 100,000
- in 2014, 99% of bacteraemia reports of *Klebsiella* spp. were identified to species level. This represented a continuing improvement in species reporting
- the rate of *Klebsiella* spp. was generally higher in males than females and among older adults (≥65 years) and infants (<1 year)
- at country level, England had the highest rate of *Klebsiella* spp. bacteraemia reports (11.30/100,000) followed by Northern Ireland (9.73) and Wales (7.82)
- within England, Greater Manchester had the highest rate of reports at 14.11/100,000 population, followed by Cumbria and Lancashire at 13.32. The lowest rate was in Thames Valley (6.55)
- antimicrobial susceptibility trends from 2010 to 2014 were examined for five classes of antibiotics
- of the two third-generation cephalosporins examined, there appeared to be marginal increases in resistance to cefotaxime and ceftazidime for *Klebsiella* spp., reaching 10% (12% for *K. pneumonia*) for each antibiotic in 2014
- resistance to the fluroquinolone ciprofloxacin was broadly stable between 2013 and 2014, reported in 9% of *Klebsiella* spp. blood culture isolates
- the five-year trend analysis showed that resistance to the aminoglycoside gentamicin increased significantly at genus level and for *K. pneumoniae*
- further increases in *Klebsiella* spp. resistance to piperacillin/tazobactam were seen, reported in 16% of isolates in 2014 (17% for *K. pneumoniae*). This may reflect the recent switch from CLSI to EUCAST MIC breakpoint from 16 to 8 mg/L for this agent
- resistance to the carbapenems remained uncommon although significant increases were seen from 0.3% (11/4,025) of *Klebsiella* spp. isolates in 2010 to 1.6% (94/5,801) in 2014
- in terms of multi-drug resistance, the most common dual resistance in *K. pneumoniae* was to third generation cephalosporins and ciprofloxacin at 18.3% of these isolates. The lowest dual resistance was for *K. oxytoca* in relation to ciprofloxacin and gentamicin (2.3%).

## Trends in the number of reports and rates

Between 2013 and 2014, the total number of *Klebsiella* spp bacteraemia reports in EWNI increased by 0.8% from 6,453 to 6,507 respectively (table 1). The total number of *Klebsiella* spp. reports has been stable since 2011, at around 6,500 *per annum*. In 2014 the majority were reported to species level (99%), representing a continuing improvement over the previous four years (range: 97%-98%).

The predominant *Klebsiella* species causing bacteraemia was *K. pneumoniae*, accounting for 80% of *Klebsiella* spp. bacteraemia reports in 2014, followed by *K. oxytoca* (19%). *K. pneumoniae* bacteraemia reports increased by 1.8% from 2013 to 2014 (from 5,086 to 5,177); over the five-year period the reports for this species increased by 13% (table 1).

Figure 1 shows trends in the rates of bacteraemia laboratory reports for *Klebsiella* species between 2010 and 2014. The annual rate of *Klebsiella* spp. bacteraemia was relatively stable around 11.0 per 100,000 resident population. The rate of bacteraemia due to *K. pneumoniae* showed more variation with an increase by 10.7% from 7.96/100,000 in 2010 to 8.81/100,000 in 2014. The rate increased by 1.8% from 2013 to 2014. The rate for *K. oxytoca* was stable throughout the study period.

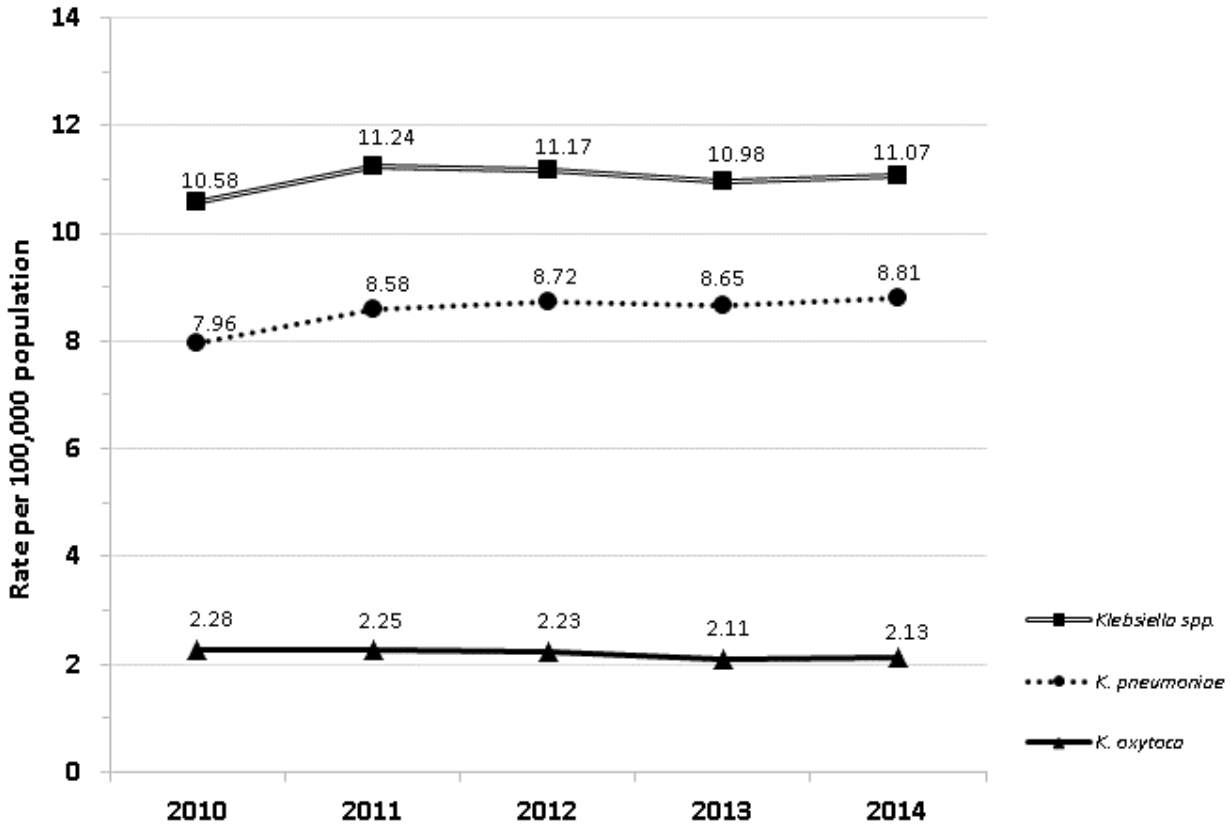
**Table 1. Reports of bacteraemia due to *Klebsiella* spp. (England, Wales and Northern Ireland): 2010 to 2014**

| | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| ***Klebsiella* spp.** | **6,083** | 100% | **6,518** | 100% | **6,525** | 100% | **6,453** | 100% | **6,507** | 100% |
| *Klebsiella pneumoniae* | 4,574 | 75.2% | 4,976 | 76.3% | 5,091 | 78.0% | 5,086 | 78.8% | 5,177 | 79.6% |
| *Klebsiella oxytoca* | 1,313 | 21.6% | 1,307 | 20% | 1,300 | 19.9% | 1,240 | 19.2% | 1,250 | 19.2% |
| *Klebsiella*, other named species | 0 | <1% | 9 | <1% | 10 | <1% | 13 | <1% | 10 | <1% |
| *Klebsiella*, species not recorded | 196 | 3.2% | 226 | 3.5% | 124 | 1.9% | 114 | 1.8% | 70 | 1.1% |

*0% in 2010 due to 0 cases; 0.1% in 2011; 0.2% in 2012; 0.2% in 2013; 0.2% in 2014

Source: PHE, 2015

**Figure 1: Rates of laboratory bacteraemia reports of *Klebsiella* spp., *K. pneumoniae* and *K. oxytoca* in England, Wales and Northern Ireland per 100,000 resident population, 2010-2014**



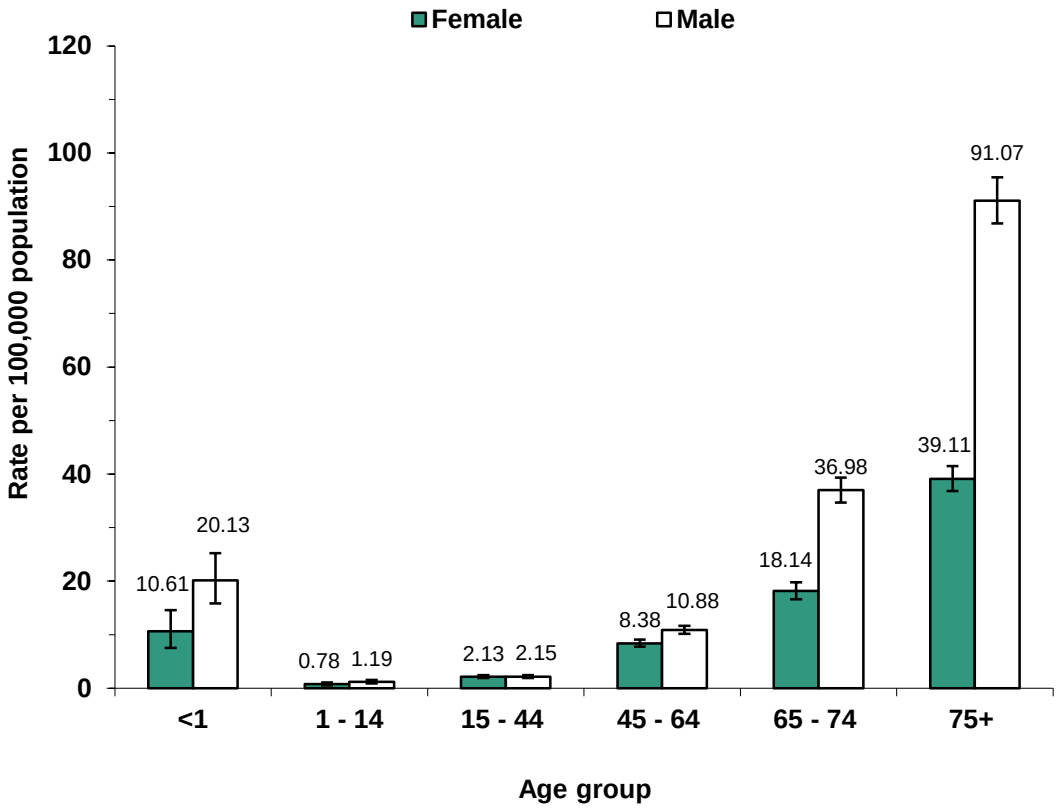

Source: PHE, 2015

## Age and sex distribution

Figures 2 to 4 show the age and sex-specific rate of bacteraemia reports in EWNI in 2014 per 100,000 resident population for *Klebsiella* spp. and the two main *Klebsiella* species i.e. *K. pneumoniae* and *K. oxytoca*. In general, the rate was higher in adults over 65 years and in infants (under one year) although the rate in the infant group was based on a relatively smaller sample size (114 *Klebsiella* spp. reports, of which 79 concerned *K. pneumoniae* and 33 *K. oxytoca*) compared to the two oldest age groups . Across all analyses, the highest rate was among patients aged 75 years or more. The rate of bacteraemia was substantially higher among males than females across all age groups except among those aged 15-44 years where the rates were very similar in male and female patients.

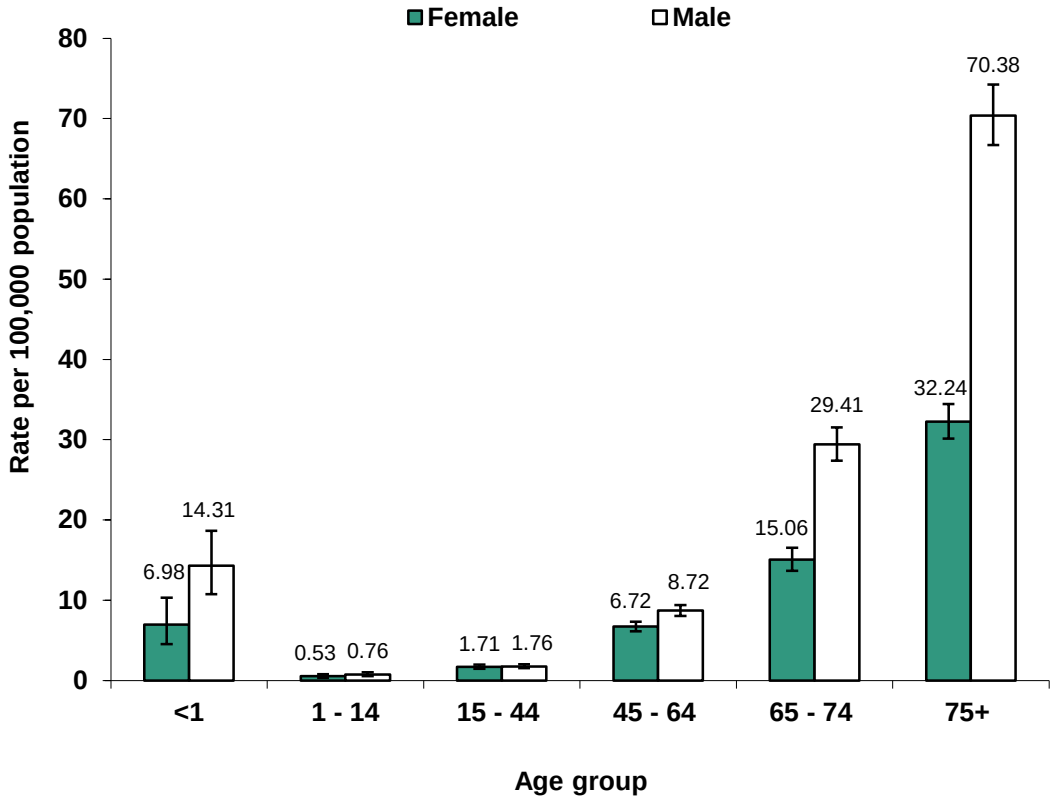
Among the oldest age group (75 years or more), the rate was two to three times higher in males than in females (figures 2-4), with incidence rate ratios of 2.33, 2.18 and 3.10 for *Klebsiella* spp., *K. pneumoniae* and *K. oxytoca* respectively.

**Figure 2. Age and sex-specific rates of *Klebsiella* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2014**



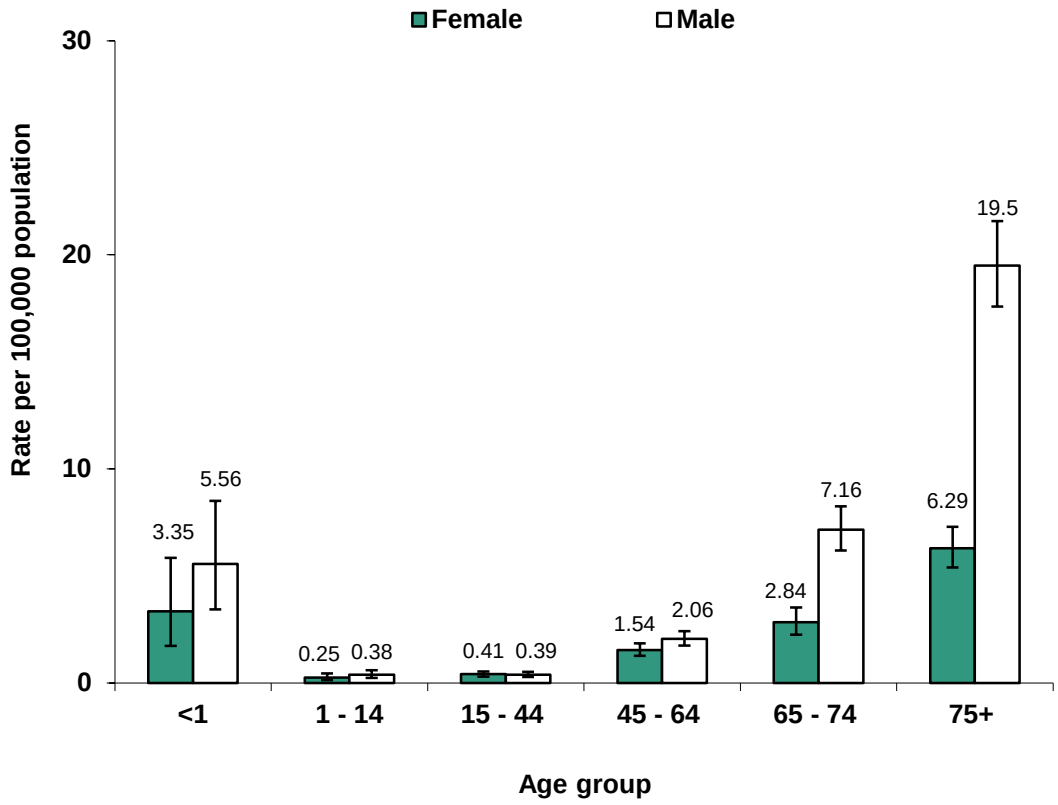

Source: PHE, 2015

**Figure 3. Age and sex-specific rates of *K. pneumoniae* bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2014**




Source: PHE, 2015

**Figure 4. Age and sex-specific rates of *K. oxytoca* bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2014**




Source: PHE, 2015

## Geographical distribution

Figure 5 shows the rate of bacteraemia based on *Klebsiella* spp. reports per 100,000 population in 2014 at country level and at English regional level (Public Health England Centres). This analysis is not corrected for variation in reporting between geographical areas.

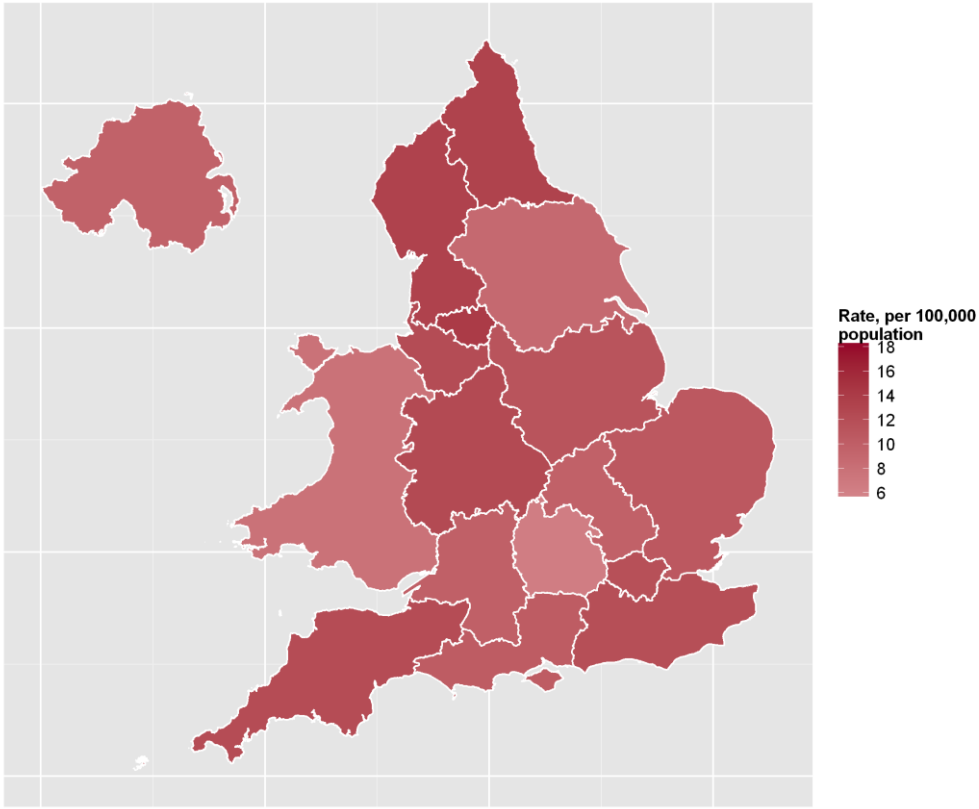
The bacteraemia rate for EWNI as a whole was 11.07/100,000 in 2014. England had the highest rate at 11.30 followed by Northern Ireland at 9.73 then Wales at 7.82.

Within England, variation in the rate between the 15 PHECs was observed. Greater Manchester had the highest rate at 14.11/100,000 population, followed by Cumbria and Lancashire at 13.32/100,000. Greater Manchester is located in the North West, a region observed to have the highest *Klebsiella* spp bacteraemia rate in previous years [3,4,5]. The lowest rate was in Thames Valley at 6.55/100,000.

The geographical variation may be explained by differences in completeness of reporting between PHECs. Local outbreaks, differences in case-mix and variation in the distribution of specialist care units may also influence these rates.

Table 2 shows the five-year trends in the rate by geography. Greater Manchester generally had the highest rates between 2010 and 2014 although the trend has been decreasing from 2011 onwards. The rate decreased between 2013 and 2014 for Cheshire and Merseyside. The lowest rates were consistently observed in Thames Valley over this five year period. Avon, Gloucestershire and Wilshire centre appears to show an increasing trend albeit the increases are small.

**Figure 5. Geographical distribution of the rate of *Klebsiella* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2014**




Source: PHE, 2015

**Table 2: Rate *Klebsiella* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2010-2014**

| Region | PHE centre | Rate per 100,000 resident population | | | | |
|---|---|---|---|---|---|---|
| | | 2010 | 2011 | 2012 | 2013 | 2014 |
| North of England | Cheshire and Merseyside | 13.00 | 13.99 | 14.85 | 14.87 | 12.27 |
| | Cumbria and Lancashire | 9.40 | 10.71 | 11.35 | 10.78 | 13.32 |
| | Greater Manchester | 13.52 | 15.04 | 14.91 | 14.70 | 14.11 |
| | North East | 13.03 | 11.44 | 12.26 | 11.91 | 13.22 |
| | Yorkshire and Humber | 11.02 | 10.48 | 10.29 | 7.83 | 8.86 |
| Midlands and East of England | Anglia and Essex | 10.58 | 10.37 | 11.17 | 10.02 | 10.84 |
| | East Midlands | 12.04 | 13.97 | 11.17 | 12.10 | 11.36 |
| | South Midlands and Hertfordshire | 8.11 | 8.17 | 9.97 | 8.81 | 9.84 |
| | West Midlands | 10.64 | 11.71 | 11.47 | 11.40 | 12.49 |
| London | London | 10.41 | 12.13 | 11.72 | 12.10 | 11.82 |
| South of England | Avon Gloucestershire and Wiltshire | 7.59 | 8.42 | 8.86 | 8.53 | 9.99 |
| | Devon Cornwall and Somerset | 12.69 | 11.30 | 11.63 | 12.19 | 12.24 |
| | Kent Surrey and Sussex | 10.39 | 10.93 | 11.45 | 12.33 | 11.95 |
| | Thames Valley | 7.02 | 8.39 | 7.44 | 6.60 | 6.55 |
| | Wessex | 9.07 | 9.22 | 8.74 | 9.74 | 10.45 |
| England | | 10.65 | 11.28 | 11.23 | 10.99 | 11.30 |
| Northern Ireland | | 11.64 | 11.91 | 11.84 | 11.97 | 9.73 |
| Wales | | 8.75 | 10.25 | 9.79 | 10.19 | 7.82 |
| England, Wales and Northern Ireland | | 10.58 | 11.24 | 11.17 | 10.98 | 11.07 |

Source: PHE, 2015

## Antimicrobial susceptibility data

Tables 3 to 5 present antibiotic susceptibility data for blood culture isolates of *Klebsiella* spp. (all species combined), *K. pneumoniae* and *K. oxytoca*. This analysis examines five classes of antibiotics: third-generation cephalosporins (cefotaxime and/or ceftazidime), carbapenems (imipenem/meropenem or ertapenem only if there was no evidence of testing for imipenem or meropenem), a fluoroquinolone (ciprofloxacin), a penicillin/beta-lactamase inhibitor combination (piperacillin/tazobactam) and an aminoglycoside (gentamicin). Table 6 shows multi-drug resistance in England in 2014 based on a defined combination of antimicrobial drugs using SGSS's AMR data.

Among *Klebsiella* spp. the most common mechanism of resistance to third-generation cephalosporins (cefotaxime or ceftazidime) is plasmid-mediated extended-spectrum β-lactamase (ESBL) production. For *Klebsiella* spp. isolates (all species), there appeared to be

marginal increases in resistance to cefotaxime and to ceftazidime from 8% in 2010 to 10% in 2014 for each agent (table 2). Similarly, for *K. pneumoniae,* marginal increases in resistance to both agents appeared (from 9% in 2010 to 12% in 2014 for each agent). The analysis for *K. oxytoca*, exhibited lower level of resistance to these agents and there did not appear to be a discernable trend based on observed data for this species.

### Table 3. Antibiotic susceptibility of *Klebsiella* spp. bacteraemia isolates, England, Wales and Northern Ireland: 2010-2014

| | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant |
| **Piperacillin/ Tazobactam** | 4,245 | 10% | 4,743 | 12% | 4,931 | 12% | 4,896 | 15% | 5,512 | 16% |
| **Imipenem/ Meropenem*†** | 4,025 | <1% | 4,484 | <1% | 4,650 | <1% | 4,585 | <1% | 5,801 | 2% |
| **Cefotaxime** | 2,793 | 8% | 3,094 | 8% | 3,170 | 9% | 3,029 | 9% | 3,490 | 10% |
| **Ceftazidime** | 3,835 | 8% | 4,208 | 8% | 4,237 | 9% | 3,984 | 9% | 4,524 | 10% |
| **Ciprofloxacin** | 4,489 | 8% | 4,908 | 8% | 5,047 | 8% | 4,926 | 9% | 5,525 | 9% |
| **Gentamicin** | 4,825 | 5% | 5,354 | 5% | 5,420 | 5% | 5,320 | 6% | 5,998 | 6% |
| **Total *Klebsiella* spp. reports** | 6,083 | | 6,518 | | 6,525 | | 6,453 | | 6,507 | |

*0.3% in 2010; 0.6% in 2011; 0.7% in 2012; 0.7% in 2013; 1.6% in 2014

† Ertapenem included only if imipenem or meropenem not tested

### Table 4. Antibiotic susceptibility of *K. pneumoniae* bacteraemia isolates, England, Wales and Northern Ireland: 2010-2014

| | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant |
| **Piperacillin/ Tazobactam** | 3,172 | 10% | 3,605 | 12% | 3,873 | 13% | 3,832 | 15% | 4,383 | 17% |
| **Imipenem/ Meropenem*†** | 3,029 | <1% | 3,417 | <1% | 3,641 | 0.8% | 3,592 | <1% | 4,591 | 2% |
| **Cefotaxime** | 2,138 | 9% | 2,410 | 9% | 2,514 | 10% | 2,412 | 11% | 2,765 | 12% |
| **Ceftazidime** | 2,889 | 10% | 3,230 | 10% | 3,335 | 11% | 3,161 | 11% | 3,573 | 12% |
| **Ciprofloxacin** | 3,366 | 9% | 3,748 | 9% | 3,957 | 10% | 3,866 | 10% | 4,407 | 11% |
| **Gentamicin** | 3,633 | 6% | 4,094 | 6% | 4,246 | 7% | 4,167 | 8% | 4,758 | 8% |
| **Total *K. pneumoniae* reports** | 4,574 | | 4,976 | | 5,091 | | 5,086 | | 5,177 | |

*0.3% in 2010; 0.7% in 2011; 0.8% in 2012; 0.7% in 2013; 1.9% in 2014

† Ertapenem included only if imipenem or meropenem not tested

**Table 5. Antibiotic susceptibility of *K oxytoca* bacteraemia isolates, England, Wales and Northern Ireland: 2010-2014**

| | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant | No. tested | % resistant |
| **Piperacillin/ Tazobactam** | 933 | 12% | 955 | 11% | 956 | 11% | 959 | 12% | 1,059 | 13% |
| **Imipenem/ Meropenem*†** | 859 | <1% | 901 | <1% | 925 | <1% | 902 | <1% | 1,137 | <1% |
| **Cefotaxime** | 585 | 4% | 603 | 4% | 607 | 5% | 574 | 5% | 673 | 2% |
| **Ceftazidime** | 814 | 2% | 820 | 3% | 838 | 3% | 758 | 3% | 896 | 1% |
| **Ciprofloxacin** | 974 | 2% | 980 | 2% | 995 | 2% | 962 | 2% | 1,041 | 2% |
| **Gentamicin** | 1,035 | 2% | 1,072 | 1% | 1,069 | 1% | 1,049 | 1% | 1,160 | 2% |
| **Total *K. oxytoca* reports** | **1,313** | | **1,307** | | **1,300** | | **1,240** | | **1,250** | |

*0% in 2010 due to 0 cases; 0.1% in 2011; 0.3% in 2012; 0.6% in 2013; 0.4% in 2014

† Ertapenem included only if imipenem or meropenem not tested

Source: PHE, 2015

The proportion of isolates reported resistant to piperacillin/tazobactam increased significantly over the five-year period for *Klebsiella* spp. isolates (from 10% in 2010 to 16% in 2014) ($p<0.0001$). This was similarly reflected in the analysis for *K. pneumoniae*, which also showed a significant increase from 10% in 2009 to 17% in 2014 ($p<0.0001$). These results are likely to reflect laboratories switching from the CLSI to EUCAST MIC breakpoint from 16 to 8 mg/L for this agent in relation to Enterobacteriaceae introduced in 2011. However there was no evidence of change in resistance to this antibiotic among *K. oxytoca* isolates ($p=0.386$).

In terms of susceptibility to ciprofloxacin, the increase in resistance between 2010 and 2014 was not statistically significant at genus level or at species level i.e. *K. pneumoniae* or *K. oxytoca* ($p=0.075$; $p=0.089$ and $p=0.112$ respectively).

Resistance to gentamicin increased significantly at genus level and for *K. pneumoniae* (both $p<0.05$); but there was no evidence of change for *K. oxytoca* ($p=0.941$). The reason for the increase at genus level is due to the increase of *K. pneumoniae* given that this species accounts for the majority of *Klebsiella* spp.

Resistance to the carbapenems remained uncommon in 2014 although increases were observed from 0.3% (11/4,025) of isolates in 2010 to 1.6% (94/5,801) in 2014. Despite the small underlying numbers, the increase was slow but steady at genus level ($p<0.0001$) and for

*K. pneumoniae* (p<0.0001) over the five-year period. No evidence of a trend was found for *K. oxytoca* reflecting the fact that resistance to carbapenems appears to be far less common in this species. At country level the majority of carbapenem-resistant isolates reported between 2010 and 2014 (n=193) were from England (183/193). At PHE centre level, the majority of these isolates were reported from laboratories in Greater Manchester at 25% (49/193) followed by London at 22% (42/193).

The increasing trend in carbapenem resistance among *Klebsiella* spp. bacteraemia isolates has been reported previously [3,4,5,6]. Although there are small underlying numbers involved, the increase among these bacteraemia isolates is of concern and warrants close vigilance given that this class of antibiotics is a powerful last-line treatment for serious infections caused by Gram-negative bacteria. Moreover these increases are occurring in the context of the emergence of resistance to these antibiotics among Enterobacteriaceae reported internationally in recent years [7,8].

Data based on all isolates referred to PHE's national reference laboratory, the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, indicate an increasing trend in carbapenemase-producing Enterobacteriaceae (CPE) from 2008, although sporadic cases were reported as far back as 2003. A total of 2,794 Enterobacteriaceae, from all specimen types, were identified as carbapenemase producing by AMRHAI between 2003 and 2013. *Klebsiella* spp. accounted for the majority of these isolates (79%), followed by *E. coli* (12%) then *Enterobacter* spp. (7%). Approximately 10% of confirmed carbapenemase producers were isolated from bacteraemia cases. AMRHAI found them variously to produce carbapenemases belonging to the KPC, OXA-48-like, NDM, VIM and IMP families. *Klebsiella* spp. are the commonest hosts of these enzymes. Although carbapenem resistance among Enterobacteriaceae in general (and particularly in *Enterobacter* spp.) may also be mediated by ESBL or AmpC production combined with impermeability (porin loss), the proportion of resistant isolates with carbapenemases is increasing.

In recognition of the importance of carbapenemase-producing Enterobacteriaceae (CPE), PHE issued a toolkit in December 2013 on the identification and management of affected patients in acute healthcare settings [9]. This toolkit includes a risk assessment to identify those individuals who should be screened for colonisation or infection with CPE as part of the routine admission procedure. A toolkit for non-acute settings is to follow.

The SGSS AMR data showed that 97% of total *Klebsiella* spp. blood culture isolates had antimicrobial susceptibility data (4,390/4,521). Multi-drug resistance was based on combinations of two different defined antibiotics (table 6). Generally dual resistance to third generation cephalosporins and ciprofloxacin was most common and combined resistance to both ciprofloxacin and gentamicin the least common. Genus-level data masked variation at species level. *K. pneumoniae* exhibited the highest resistance per combination category and *K. oxytoca* tended to exhibit the lowest resistance levels. Among *K. pneumoniae* bacteraemia isolates, the most common dual resistance was to third generation cephalosporins and ciprofloxacin (18.3%). This result may be due to testing bias as the resistance analysis based on data by individual agent yielded lower resistance rates. The least common dual resistance was for *K. oxytoca* in relation to ciprofloxacin and gentamicin at 2.3% of isolates. Resistance to third generation cephalosporins, ciprofloxacin, gentamicin and meropenem was uncommon (<1%) at genus level (18/3,628) and at species level i.e. *K. pneumoniae* (17/2,853) and *K. oxytoca* (0/730) (data not shown). The low level of combined resistance based on these four agents is likely to reflect the fact that meropenem resistance is uncommon.

**Table 6. Multi-drug resistance among isolates of bacteraemia due to *Klebsiella* spp., *K. pneumoniae* or *K. oxytoca*, England, 2014**

| | 3rd-G cephalosporin* and ciprofloxacin | | 3rd-G cephalosporin* and gentamicin | | Ciprofloxacin and gentamicin | |
|---|---|---|---|---|---|---|
| | Total No. isolates tested | % Resistant | Total No. isolates tested | % Resistant | Total No. isolates tested | % Resistant |
| ***Klebsiella* spp.** | 3,836 | 15.6 | 3,826 | 13.6 | 4,221 | 11.4 |
| ***K. pneumoniae*** | 3,009 | 18.3 | 3,001 | 15.9 | 3,343 | 13.6 |
| ***K. oxytoca*** | 781 | 4.5 | 779 | 4.6 | 824 | 2.3 |

*cefotaxime or ceftazidime or both

Source: PHE, 2015

For advice on treatment of antibiotic-resistant infections due to these organisms or for reference services including species identification and confirmation of sensitivity testing results, laboratories should contact PHE's AMRHAI Reference Unit in London [10].

**Acknowledgements**

These reports would not be possible without the weekly contributions from microbiology colleagues in laboratories across England, Wales, and Northern Ireland, without whom there would be no surveillance data. Feedback and specific queries about this report are welcome and can be sent to: mailto:hcai.amrdepartment@phe.gov.uk

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